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Published in:

The International Journal of Cardiovascular Imaging

DOI:

10.1007/s10554-021-02263-7

Publication date:

2021

Document version:

Final published version

Citation for pulished version (APA):

Piri, R., Lici, G., Riyahimanesh, P., Gerke, O., Alavi, A., & Høilund-Carlsen, P. F. (2021). Two-year change in ^{18}F -sodium fluoride uptake in major arteries of healthy subjects and angina pectoris patients. *The International Journal of Cardiovascular Imaging*, 37(10), 3115-3126. <https://doi.org/10.1007/s10554-021-02263-7>

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Two-year change in ¹⁸F-sodium fluoride uptake in major arteries of healthy subjects and angina pectoris patients

Short title: 2-year change in ¹⁸F-sodium fluoride uptake in major arteries

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9 **ABSTRACT**

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11 **Purpose:** To examine 2-year changes in carotid and aortic ¹⁸F-sodium fluoride (NaF) uptake in both
12 healthy controls and angina pectoris patients.
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15 **Methods:** Twenty-nine healthy subjects and 20 angina pectoris patients underwent 90-min NaF-
16 PET/CT twice two years apart. The carotids and three sections of the aorta (arch, thoracic, abdominal)
17 were manually segmented. NaF uptake was expressed as the mean and total standardized uptake values
18 without and with partial volume correction (SUV_{mean}, SUV_{total} and pvcSUV_{mean}, pvcSUV_{total}).
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21 **Results:** Insignificant tendencies were higher NaF uptake in angina patients at both time points with
22 less uptake in healthy subjects and higher uptake in angina patients after 2 years. Thus, aortic
23 pvcSUV_{mean} of angina patients was 1.14±0.35 and 1.29±0.71 at baseline and after 2 years vs.
24 0.99±0.31 and 0.95±0.28 in healthy subjects. A similar pattern was observed for the carotid
25 pvcSUV_{mean}. NaF uptake at baseline could not predict a change in CT-calcification after 2 years. NaF
26 uptake in all parts of the aorta correlated positively with age.
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29 **Conclusions:** There was an insignificant, but consistent, tendency for slightly higher arterial NaF
30 uptake in the angina group indicating more ongoing microcalcification at both time points in patients
31 than healthy subjects. The 2-year changes were in both groups very small suggesting that the
32 atherosclerotic process is slow, albeit with a tendency of slight decreases among healthy controls and
33 slight increases in angina patients despite statin therapy in half of these.
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37 **Keywords:** ¹⁸F-sodium fluoride, NaF, microcalcifications, positron emission tomography/computed
38 tomography, atherosclerosis, disease progression
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Declarations

Author Contribution

AA and PFHC conceived and planned the experiments. RP, GL and PR carried out the experiments. RP analyzed images and generated results. RP, OG, AA and PFHC contributed to the interpretation of the results. RP took the lead in writing the manuscript. PFHC supervised the project. All authors provided critical feedback and helped shape the research, analysis and manuscript.

Funding sources

The study was partly funded through a PhD scholarship to Reza Piri by the University of Southern Denmark, Odense, Denmark.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Abbreviations

cSUV Corrected standardized uptake value

CT Computed tomography

CVD Cardiovascular disease

FDG 18F-fluorodeoxyglucose

FRS Framingham Risk Score

NaF 18F- sodium fluoride

PET Positron emission tomography

ROI Region of interest

SUV Standardized uptake value

VOI Volume of interest

Introduction

With increasing life expectancy and proportion of older individuals in the population, there is a growing concern about chronic morbidities such as cardiovascular diseases (CVD). Despite the significant decline in mortality from coronary heart disease and stroke during several decades, CVDs remain the number one cause of mortality worldwide [1]. The cause of decline is probably multifactorial, fueled by progress in both prevention and treatment, including widespread use of statins to lower circulating cholesterol levels and timely use of thrombolysis and stents in acute coronary syndrome. However, many questions about this decline remain. There is evidence that the rate of decline may have abated and may even be showing early signs of reversal in some population groups [2]. Thus, CVDs are one of the most challenging fields for health care systems, in particular, because symptoms of CVDs tend to appear late in the course of the disease, meaning that treatments must be directed at alleviating symptoms or complications rather than prevention.

This rather long asymptomatic phase of CVDs provides an excellent chance to counteract detectable components of CVD [3-4]. However, diagnosing CVD early in its course is also challenging because atherosclerosis, as the main underlying cause of CVD, must be developed enough to be detected using computed tomography (CT) or magnetic resonance imaging [5]. Hopefully, this limitation may be overcome by using positron emission tomography (PET), offering detection of molecular components of atherosclerosis way before it further develops. In this regard, targeting inflammation or microcalcification as initiation points of atherosclerosis [6] may make PET an effective modality to detect early-phase atherosclerosis [7].

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5 Initially, ^{18}F -fluorodeoxyglucose (FDG) was utilized to detect increased glucose uptake
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7 indicating inflammation [8]; however, FDG uptake fluctuation during the course of CVD could make
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9 detection and follow-up of atherosclerosis challenging [9]. This limitation might be overcome by
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11 targeting micro-calcifications instead using ^{18}F -sodium fluoride (NaF), not only because calcium
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13 depositions are somehow correlated with inflammation [10] but also because they tend to have a more
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15 steady presence that might predict CVDs better [11]. It has been shown that patients with suspected
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17 CVD tend to have increased NaF uptake in the coronary arteries compared to healthy individuals [12].
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19 Although it has been demonstrated that NaF uptake increases with age in the vascular system [13], it is
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21 not known, how microcalcification varies between healthy individuals and those with higher CVD risk
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23 and how it changes over time. Therefore, we mapped the occurrence and extent of NaF uptake in the
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25 carotids and the aorta in a cohort of healthy individuals and patients evaluated for angina pectoris at
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27 baseline and at follow-up after two years.
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39 **Materials and Methods**

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42 This study was part and continuation of the ‘Cardiovascular Molecular Calcification Assessed by ^{18}F -
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44 NaF PET/CT (CAMONA)’ study, conducted 2012-2014 [11], approved by the Danish National
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46 Committee on Health Research Ethics (s-20120056), and registered at ClinicalTrials.gov
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48 (NCT01724749). CAMONA was carried out in accordance with the Declaration of Helsinki. All study
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50 participants provided written informed consent.
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58 *Participant Selection*

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5 CAMONA included 89 healthy individuals with low CVD risk who were recruited via a local
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7 advertisement or from the blood bank at the Odense University Hospital, Odense, Denmark.
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9 Individuals with no history of malignant diseases, immunodeficiency syndromes, autoimmune
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11 diseases, illicit drug use, alcohol abuse or CVDs were considered healthy and were eligible for
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13 inclusion. Adults were preselected by age and gender to make sure a balanced inclusion of both
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15 genders aged 20–29, 30–39, 40–49, 50–59, and 60 years or older was guaranteed. Furthermore, 50
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17 patients suspected of having angina pectoris who were referred to the Department of Cardiology at the
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19 Odense University Hospital for coronary angiography were included.
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28 *Study Design*

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32 The included patients were asked to fill a questionnaire about alcohol consumption, smoking habits,
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34 past medical history, familial history, and current medical status. Blood pressure after at least 30
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36 minutes of rest was measured three times in the supine position. The mean of the last two
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38 measurements was recorded as the systolic and diastolic blood pressure. Laboratory tests included total
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40 serum cholesterol, serum low-density lipoprotein, serum high-density lipoprotein, serum triglycerides,
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42 fasting plasma glucose and glycated hemoglobin, and glomerular filtration rate, which was calculated
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44 using the Modification of Diet and Renal Disease equation [14]. The 10-year risk of developing CVD
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46 was estimated using the Framingham Risk Score (FRS) based on age, gender, systolic blood pressure,
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48 total serum cholesterol, serum HDL cholesterol, smoking habit, and treatment for hypertension [15].
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50 Then they were offered a whole-body NaF-PET/CT scan at baseline and after two years of follow-up
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52 performed at the same PET/CT scanner and at approximately the same time of the day (morning or
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54 noon). Of all initially included patients, 29 healthy individuals and 20 patients with angina pectoris
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5 attended the 2-year follow-up. So, this subgroup of patients was examined to inspect the change
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7 prospectively during two years in NaF uptake in major arteries, including the carotids and the arch,
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9 thoracic, and abdominal parts of the aorta.
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16 *NaF-PET/CT Protocol*

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20 NaF-PET/CT imaging was performed according to previously published methods [16] on hybrid
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22 PET/CT systems (General Electric Healthcare using Discovery PET/CT. All participants underwent
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24 PET/CT imaging 90 minutes after injection of approximately 2.2 MBq/kg (max 400 MBq) NaF. The
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26 acquisition time was 2.5 minutes per bed position. PET/CT system specifications and parameters of
27
28 image reconstruction are summarized in the Supplemental Table 1. The 3D acquisition of total-body
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30 PET images and reconstruction of them into transverse, coronal and sagittal slices was made by an
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32 iterative reconstruction algorithm (VUE Point; GE Healthcare). The correction of PET images for
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34 random, scattered coincidences, attenuation and anatomic directions was done by implanting
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36 transmission maps produced by a 64-slice CT scan as follows (120 kV, 200 mA, 16 x 2.5 mm
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38 collimation, 0.5 seconds per rotation).
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48 *Image Analysis*

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52 All scans at baseline and follow-up were analyzed and quantified independently, the reader was
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54 unaware of the participants' demographic and clinical features. ROVER software version 3.0.4 (ABX
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56 GmbH, Radeberg, Germany) was used for quantitative analysis. Initially, PET and CT images were
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5 reregistered using DICOM information, allowing us to improve the diagnostic accuracy of both
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7 modalities and optimizing the outlining of aortic segments, and then imported into the software. If
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9 necessary, additional adjustment of images was made by modification of PET images in transverse,
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11 coronal and sagittal planes considering the CT images as the reference point.
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16 The volume of interest (VOI) was formed by stacking manually defined regions of interest (ROIs)
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18 using a 5 mm width brush in CT images for each participant. The VOIs included left carotid and right
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20 carotid, arch of aorta, thoracic aorta, and abdominal aorta. The arch of the aorta was defined as aorta
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22 above the lower level of T5 in a transaxial view until the aortic valve. The carotids were defined from
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24 the branching initiation (branching from aorta for left carotid and brachiocephalic artery for right
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26 carotid) until the bifurcation (including itself). The thoracic aorta was defined as aorta between the
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28 inferior edge of T5 to T12. The abdominal aorta was defined as aorta between the lower level of T12
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30 until the beginning of the bifurcation. A sample of segmented NaF-PET/CT images, including VOIs in
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32 3-dimensional planes, is shown in Figure 1. The manual ROI determination was done in a manner that
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34 would contain the whole carotid or aortic wall (intima, media and adventitia), excluding the vertebral
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36 bones and their uptake halo from inclusion in defined ROIs. Therefore, in some transaxial slices, where
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38 the aorta was adjacent to the vertebral body, the ROI was defined with a lunar shape, unlike all other
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40 slices in which the ROI was circular.
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48 Performing a quantitative assessment of PET scans was done by generating standardized uptake
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50 values (SUVs) of the VOIs, adjusted to body weight. After segmentation of each ROI, the recorded
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52 NaF uptake was expressed as SUV_{mean} (average SUV of all voxels within VOI), SUV_{max} (the
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54 highest SUV of all voxels in the VOI), SUV_{total} (sum of the SUVs of all voxels), and as the
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56 corresponding measures corrected for partial volume effect (i.e., pvcSUV_{mean} and pvcSUV_{total}) as
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5 described by Hofheinz et al. [17] The measurement of NaF uptake was, therefore, performed in two
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7 automated steps, first by approximation of the actual object boundaries with a threshold-based method
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9 and determination of the total activity in ROI and then determining activity fraction, which is measured
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11 outside the ROI due to spill-out. With this correction approach, accurate knowledge of image
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13 resolution is not necessary as it is, for instance, with deconvolution techniques [18-19]. The
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15 measurement unit was MBq/ml. Also, the CT-related variable mean density (CTmean) expressed in
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17 Hounsfield units was extracted in all corresponding VOIs.
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23 The reproducibility of quantifying arterial wall NaF uptake was reported earlier [20]. By repeat
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25 determination of aortic uptake performed in 25 randomly selected scans after several months and
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27 without knowledge of prior results, one observer (RP) found in the three segments of the aorta a
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29 variation in SUV values of maximally 6 percent.
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37 *Statistical Analysis*

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40 Descriptive statistics were expressed as frequency (percentage), mean \pm standard deviation or median
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42 (minimum-maximum). Mann-Whitney U and Fisher's exact test were used to compare demographic,
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44 laboratory, and PET/CT variables between healthy and angina groups. Intragroup comparisons over
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46 time were performed with Wilcoxon matched pairs signed rank sum test, and change over time was
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48 shown as the mean of estimated differences. Aside from the comparison of control and angina groups
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50 and in order to compare NaF uptake in different major arteries within groups, Friedman's test was
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52 used, in which the Wilcoxon matched pairs signed rank sum test was performed post hoc. Finally, the
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54 non-parametric Spearman's correlation test was used to examine for correlation between PET/CT
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5 variables and age, then Fisher's r-to-z transformation method was applied to compare them [21]. NaF
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7 uptake was plotted against age in a scatter plot, supplemented by fitted lines from linear regression for
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9 each group of subjects. A p-value of less than 0.05 was considered statistically significant. All
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11 statistical analyses were performed using SPSS 19.0 (SPSS Inc., Chicago, IL, USA).
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19 **Results**

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22 Participants' demographics, laboratory test results, medical history and medications are shown in Table
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24 1. The two groups did not significantly differ regarding age, gender, weight and height. Participants in
25
26 the angina group tended to have higher 10-year FRS compared to those in the healthy group; besides,
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28 other differences in laboratory tests, medical history, familial history, and medications were observed.
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30 With regard to medication, there was a noteworthy change in that 11 angina pectoris patients had statin
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32 medication at 2-year follow-up compared to only 5 at baseline.
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38 Baseline NaF uptake and density in the carotids and aorta (Tables 2 and 3, respectively) were
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40 compared between healthy and angina groups. With few exceptions, at baseline, the carotid NaF uptake
41
42 was slightly higher in angina pectoris patients than in controls. The same trend was invariably present
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44 in all three sections of the aorta (Table 2). After 2 years, there was a tendency for a slight decline in
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46 NaF uptake (pvcSUVmean) in both the carotids and the three aortic segments of healthy controls,
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48 whereas the opposite trend was present in angina pectoris patients. In these, there was, on average, a
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50 slight increase in NaF uptake in all segments: by 2 percent in the carotids (1.64 ± 0.44 vs. 1.67 ± 0.63), 19
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52 percent in the aortic arch (1.15 ± 0.42 vs. 1.37 ± 0.86), 12 percent in the thoracic aorta (1.04 ± 0.35 vs.
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54 1.16 ± 0.6) and 6 percent in the abdominal aorta (1.31 ± 0.44 vs. 1.39 ± 0.82). Mean NaF uptake in the
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5 different sections of the carotids (Figure 2a) and in the aorta (Figure 2b) at baseline and follow-up are
6 shown in Figure 2. In almost all VOIs, mean NaF uptake decreased in healthy individuals over 2 years,
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8 while this trend was opposite in patients with angina.
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13 Baseline and follow-up density of the major arteries quantified by CT scan did not change
14 significantly after two years of follow-up (Table 3). At baseline, there was a tendency for lower CT
15 density in angina patients than healthy controls, except for clearly higher density in the abdominal aorta
16 of angina patients. At 2-year follow-up, there was a slightly higher density in the abdominal aorta in
17 both groups, but otherwise no clear changes.
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26 Since the arteries' volume increased significantly with age, SUV_{total} was age-dependent. The
27 correlation of NaF uptake and density with age in major arteries among all participants is shown in
28 Table 4. NaF uptake in all segments of aorta, namely pvcSUV_{mean}, had a significantly positive
29 correlation with age. Also, maximum density in almost all the major arteries was positively correlated
30 with age. Baseline SUV_{mean} correlated with change in CT_{mean} in the arch of aorta ($r=0.43$, $p=0.003$)
31 but not in the left carotid ($r=-0.03$, $p=0.83$) or right carotid ($r=0.13$, $p=0.36$), abdominal aorta ($r=0.09$,
32 $p=0.55$) and thoracic aorta ($r=-0.02$, $p=0.88$),.
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44 A simple linear regression was applied to predict pvcSUV_{mean} in the whole aorta based on the
45 participants' age (Figure 3). A significant regression equation was found ($F(1,47)=10.721$, $p=0.002$),
46 with an R^2 of 0.18. Participants' predicted pvcSUV_{mean} in the aorta was equal to $0.44 + 0.012$ age,
47 where age was measured in years. In stratified analyses by group, the same linear regression was also
48 significant in each group (see Supplemental Table 2).
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Discussion

Statement of Principal Findings

There was a statistically insignificant trend for higher NaF uptake in the carotids and the aorta of angina patients than healthy subjects. Thus, all recorded mean NaF activity values were higher in the angina patients (Table 2). This difference was most prominent in the arch and abdominal aorta. There was a similarly consistent trend for slightly lower mean NaF uptake after two years in the healthy group and slightly increased uptake in the angina group (Table 2), even if more angina patients received statin therapy during the follow-up period, i.e., 11 out of 20 compared to only 5 out of 20 at baseline. This change in the angina group during follow-up was in keeping with the positive correlation between age and NaF uptake in these major arteries. On the whole, our results indicate that early-phase atherosclerotic microcalcification is a slow process showing little progress over a time span of 2 years. Surprisingly, arterial macrocalcification, measured in Hounsfield units in the same arterial segments, did neither show any obvious changes during the same time span, and, in fact, there was slightly lower calcification density in angina patients at baseline than in healthy controls, suggesting variation in CT-measurements or macrocalcification or both.

Strengths and Weaknesses of the Study

A main strength of the current study was that we examined both groups prospectively, while a good deal of the previous reports were post-hoc analyses of NaF-PET/CT scans performed for other purposes, in particular search for skeletal metastases in cancer patients on various treatment regimens

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5 including chemo- and radiotherapy [22]. The age of our study population ranged from 21 to 75 years,
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7 providing a suitable age span to investigate changes in arterial NaF uptake with age, and our repeat
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9 PET/CT scans were made with the same scanner in each patient and solely to elucidate potential
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11 variations with time.
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16 There were also significant limitations, the most critical one being technical in that even with
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18 reasonably new PET imaging technology, the spatial resolution of output images is low compared to
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20 the size of the arterial walls examined, which significantly hampers manual segmentation. Furthermore,
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22 proper co-registration of PET and CT components are often not present, meaning that PET and CT
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24 images must be aligned once again for segmentation of the separate VOIs. Another PET-related
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26 challenge is the fact that NaF uptake in the defined background VOI may vary significantly even by
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28 few millimeters of dislocation, when one tries to select the VOI with the least NaF uptake. This is the
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30 main reason why we chose not to calculate target-to-background values as an expression of NaF
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32 uptake. Similarly, the choice of VOI and the algorithm used for partial volume correction is
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34 challenging and may cause unexpected variation in the partial volume corrected parameters, which,
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36 however, appears not to be as critical due to the much higher numbers. The delineation of smaller
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38 arteries such as the carotids using CT without venous contrast is very difficult because of the
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40 resemblance of carotids' density and adjacent anatomical structures in some transaxial slices, in which
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42 the exact location of the artery could only be determined with guidance from upper or lower slices.
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51 In addition, there is some uncertainty with repeated manual segmentation, whereas repeated
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53 segmentation of the same scans with the AI approach yields exactly the same results. The differences at
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55 repeat manual segmentation of three parts of the aorta, i.e., the arch and the thoracic and abdominal
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5 parts were in our hands 0.4-6 percent as reported elsewhere [20], while we do not have these data for
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7 the carotids.
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10 A further limitation, which may have affected the comparison between groups, was the small
11 study population. Moreover, patients in the angina group were only suspected of having CVD at the
12 time of the baseline scan and, therefore, they might not carry a very high CVD risk rendering the
13 difference between groups correspondingly smaller. It may be that the modest changes observed were
14 an expression that it was the most agile healthy subjects and the least ill angina pectoris patients, who
15 attended the 2-year follow-up, and that, thus, the limited material was not representative of all the
16 original material. We cannot deny that and only state that the arteriosclerotic process, assessed by
17 repeat NaF-PET/CT scans, is slow and more variable than expected.
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34 *Strengths and Weaknesses in Relation to Other Studies*

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38 Atherosclerosis is mostly known as an inflammatory disease of the arterial wall [23], which is the
39 plausible reason why FDG was the first successful PET tracer utilized to characterize atherosclerosis
40 [24-25]. Although it could detect inflammation, it was unspecific for the detection of atherosclerosis
41 and tracing glucose utilization in the artery wall and, as mentioned, has been found to be rapidly
42 changing [9], limiting the possibility of making longitudinal studies. Therefore, NaF was proposed to
43 detect microcalcification as a sign of incipient atherosclerosis [22, 26], which may not be as rapidly
44 changing. *In vitro* and *in vivo* studies have demonstrated that arterial wall NaF uptake is due to
45 adsorption to calcium deposits [27-28]. Likewise, high NaF uptake appears to be more consistently
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5 associated with different CVD risk factors [7]. These shreds of evidence appear to be in line with our
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7 study, where NaF uptake was higher in the angina than the healthy group.
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11 There is no standardization of how to quantitate arterial tracer uptake. This was highlighted by
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13 Huet at al. already in 2015. They identified in 49 articles 53 different acquisition protocols, 51
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15 reconstruction protocols, and 46 quantification methods to characterize atherosclerotic lesions from
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17 FDG PET scans [29]. As of today, the situation is unaltered and the same goes for arterial NaF uptake.
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19 The target-to-background ratio (TBR) has become a popular measure of arterial uptake of PET tracers
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21 [30]. However, it is a small number and it differs only slightly from the background activity which is
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23 defined in various ways by various authors. Often, the blood pool activity is used as denominator, but
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25 this is critical, since as it varies with closeness to nearby bones [31]. TBR is particularly unfortunate
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27 when it comes to measuring change over time, because it is a ratio of two independent measurements
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29 with each their sources of error. In repeat measurements these come into play twice, which makes it
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31 much more difficult to detect statistically significant differences – a circumstance described in detail
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33 elsewhere [32]. For these reasons we did not report TBR values but the more direct measurement
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35 variables presented here.
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43 Arterial calcification in the shape of micro- or macrocalcifications is considered a hallmark of
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45 aging, especially in the presence of diabetes, hypertension and chronic renal diseases [33]. Likewise, it
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47 has been shown in many studies that NaF uptake in arteries increases with age. This correlation was
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49 also present in our study, where age was positively correlated with NaF uptake in the examined
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51 arteries. However, although statistically significant, the correlation was weak. Nonetheless, we
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53 expected to find the same increase in NaF uptake after two years, but it was not present in the healthy
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55 group and surprisingly small in the angina group. In fact, the finding of slight decline in the healthy
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5 subjects was unexpected. However, the same trend we also found for the CT-detectable changes is in
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7 line with what has been reported by Meirelles et al. with regard to change in arterial FDG uptake over
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9 time [9].
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16 *Meaning of the Study: Possible Mechanisms*

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20 The mentioned findings seem to suggest that the arteriosclerotic process is somewhat more volatile and
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22 varied than one might think, at least in the early, non-symptomatic, stages, albeit with a more constant,
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24 but still slow, progression in angina pectoris patients. A probable reason for the small difference
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26 between our two groups was that members of the angina group were only suspected of having CVD
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28 when entering the CAMONA study, and therefore may not have been at very high risk. A more
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30 significant reason might be the fact that more than half the angina patients were on statin therapy after
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32 two years. Statins are found to be effective in decreasing inflammation in artery walls, which is
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34 detectable by FDG-PET [34-36] and possibly also by means of NaF-PET as used in the current study.
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36 If this is true, it may reflect that early atherosclerotic changes are reversible, but to what extent remains
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38 unknown until large prospective trials in very early stage atherosclerosis have been conducted. Another
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40 explanation for the limited change in NaF uptake could be that NaF is mainly a microcalcification
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42 tracer rather than a calcium deposition tracer. Thus, in a study by Fiz et al. on the correlation between
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44 calcification density and mineral metabolic activity through NaF uptake, it was concluded that NaF-
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46 PET is mostly suitable for the detection of atherosclerosis in its early phase because NaF retention
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48 progressively decreases by increased calcification density [37]. In other words, NaF uptake among
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50 patients in our angina group could have been damped by increases in calcification density during two
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5 years. However, according to Table 3, the calcification density process appears also to be a very
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7 protracted one, and progression in calcification was not reflected by baseline NaF uptake.
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10 11 12 13 14 *Unanswered Questions and Future Research*

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17 It is unclear whether changes in NaF uptake reflect only changes in arterial wall microcalcification or
18 whether it heralds beginning or developing CT-detectable macrocalcification. Animal experiments
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20 indicate that this might indeed be the case [38]; however, whether the same is true humans is not yet
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22 known. Therefore, long-term follow-up and interventional imaging studies are direly needed to
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24 investigate the time dependency and inter-relationship between molecular and macroscopic features of
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26 atherosclerosis. New developments including total body PET [39] will overcome current challenges in
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28 quantification due to misalignment and insufficient spatial resolution. Moreover, according to our
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30 experience with artificial intelligence (AI)-based interpretation of PET/CT scans this approach
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32 significantly shortens the processing time and will due to a very good reproducibility undoubtedly
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34 make it possible to measure even relatively small changes over time [20].
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45 46 **Conclusions**

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49 Our prospective 2-year follow-up study indicated that the atherosclerotic process is slow and variable
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51 in both healthy subjects and angina pectoris patients, albeit with an insignificant tendency for slightly
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53 higher NaF uptake in the angina group, more consistently so in the arch and abdominal aorta than in the
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55 carotid arteries and the thoracic aorta. The 2-year changes in the angina group may have been
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5 somewhat blunted by statin therapy. Larger, prospective studies with longer follow-up periods are
6 warranted to elucidate in more detail the time-dependent relationship between arterial wall NaF uptake
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8 and atherosclerosis development.
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Figure Legends

Fig. 1 Combined NaF-PET/CT images with the defined volumes of interest in transverse (a), coronal (b) and sagittal (c) planes.

Fig. 2 Average SUVmean in healthy individuals and patients with angina categorized in the carotids (a) and aorta (b). *Solid bars* indicate baseline NaF uptake and *striped bars* indicate follow-up uptakes. Almost in all VOIs, average SUV mean had decreased slightly after two years in healthy individuals, whereas it had increased slightly in angina patients.

Fig. 3 Linear regression model for prediction of corrected SUVmean in aorta by the participants' age (black line) ($F(1,47)=10.721$, $p=0.002$, $R^2=0.18$). Furthermore, Linear regression models for the same prediction in healthy (blue line) and angina groups (red line) were also statistically significant (see Supplemental Table 2).

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Table 1 Participants' demographics, laboratory tests, medical history, familial history, and medications.

| Variables | | Group | | P value |
|---|-----------------------------------|-------------------|----------------------|--------------|
| | | Healthy (n=29) | Angina (n=20) | |
| Sex | Male (%) | 16 (55.1) | 10 (50) | 0.72 |
| | Female (%) | 13 (44.8) | 10 (50) | |
| Age (year) | | 51 (21-75) | 57 (23-67) | 0.75 |
| Body mass index (kg/m ²) | | 27.17±5.07 | 27.02±5.11 | 0.79 |
| White blood cell (10 ³ cells/ml) | | 5.79±1.36 | 7.12±2.24 | 0.041 |
| Systolic blood pressure (mmHg) | | 132.12±19.98 | 132.45±20.62 | 0.89 |
| Diastolic blood pressure (mmHg) | | 78.19±10.24 | 80.53±8.21 | 0.38 |
| Total cholesterol (mmol/L) | | 5.08±0.78 | 5.64±1.01 | 0.06 |
| Low-density lipoprotein (mmol/L) | | 3.24±0.66 | 3.69±0.89 | 0.08 |
| High-density lipoprotein (mmol/L) | | 1.38±0.37 | 1.38±0.33 | 0.98 |
| Triglyceride (mmol/L) | | 1.03±0.56 | 1.27±0.81 | 0.43 |
| Homocysteine (µmol/L) | | 8.13±2.42 | 11.21±3.81 | 0.002 |
| Fasting blood glucose (mmol/L) | | 5.68±0.47 | 5.71±0.44 | 0.98 |
| Hemoglobin A1c (mmol/L) | | 34.66±4.71 | 37.37±2.54 | 0.009 |
| C-reactive protein (mg/L) | | 1 (1-8) | 1.8 (1-18) | 0.18 |
| Fibrinogen (µmol/L) | | 9.1 (6.6-82) | 10.3 (7.1-15.2) | 0.11 |
| Creatinine (µmol/L) | | 77.38±10.2 | 84.79±19.38 | 0.17 |
| 10-year Framingham score | | 7 (0.4-30) | 12.2 (1.5-30) | 0.036 |
| Medical history | Alcohol (%) | 25 (86.2) | 18 (90) | 0.69 |
| | Smoking (%) | 1 (3.4) | 5 (25) | 0.024 |
| | Hypercholesterolemia (%) | 2 (6.9) | 7 (35) | 0.013 |
| | Peripheral artery disease (%) | 0 (0) | 2 (10) | 0.08 |
| | Cardiovascular disease (%) | 0 (0) | 2 (10) | 0.08 |
| | Hypertensive vascular disease (%) | 0 (0) | 4 (20) | 0.012 |
| Medications | Antihypertensive medication (%) | 0 (0) | 7 (35) | 0.001 |
| | Statins (%) | 0 (0) | 5 (25) | 0.001 |

ACE: Angiotensin converting enzyme.

| Table 2 NaF uptake in major arteries among the participants | | | | | | | | |
|---|----------|--------------------|---------------------|--------------|---------------------|---------------------|---------|-----------------------------|
| | | Healthy (n=29) | | | Angina (n=20) | | | Baseline Healthy vs. Angina |
| | | Baseline | Follow up | P-value | Baseline | Follow up | P-value | |
| Left carotid | Mean | 0.95±0.18 | 0.91±0.19 | 0.17 | 0.98±0.28 | 0.98±0.31 | 0.64 | 0.85 |
| | pvcMean | 1.43±0.23 | 1.34±0.27 | 0.08 | 1.5±0.44 | 1.53±0.51 | 0.87 | 0.87 |
| | Max | 2.74±0.66 | 2.52±0.5 | 0.053 | 2.68±0.62 | 2.69±1.05 | 0.952 | 0.84 |
| | Total | 10.36±2.29 | 9.85±2.28 | 0.27 | 10.31±3.17 | 10.36±3.49 | 0.78 | 0.73 |
| | pvcTotal | 15.59±2.99 | 14.51±3.09 | 0.17 | 15.78±4.7 | 16.19±5.82 | 0.81 | 0.95 |
| Right carotid | Mean | 0.99±0.2 | 0.95±0.2 | 0.16 | 1.05±0.31 | 1.09±0.4 | 0.95 | 0.82 |
| | pvcMean | 1.62±0.35 | 1.44±0.36 | 0.001 | 1.84±0.56 | 1.88±0.97 | 0.15 | 0.2 |
| | Max | 2.76±0.72 | 2.29±0.47 | 0.005 | 2.73±0.58 | 2.86±1.21 | 0.809 | 0.83 |
| | Total | 8.55±2.09 | 8.24±1.86 | 0.39 | 8.26±2.61 | 9.29±4.05 | 0.2 | 0.44 |
| | pvcTotal | 13.83±3.09 | 12.39±3.09 | 0.005 | 14.31±3.81 | 15.68±7.44 | 0.97 | 0.81 |
| Carotids | Mean | 0.97±0.17 | 0.93±0.19 | 0.11 | 1±0.28 | 1.02±0.34 | 0.94 | 0.87 |
| | pvcMean | 1.52±0.27 | 1.39±0.29 | 0.008 | 1.64±0.44 | 1.67±0.63 | 0.6 | 0.55 |
| | Max | 3±0.77 | 2.64±0.45 | 0.008 | 2.92±0.58 | 3.01±1.16 | 0.936 | 0.84 |
| | Total | 18.9±4.01 | 18.09±3.84 | 0.3 | 18.57±5.59 | 19.66±7.39 | 0.66 | 0.42 |
| | pvcTotal | 23.42±5.36 | 26.9±5.57 | 0.022 | 30.09±7.9 | 31.87±12.66 | 0.93 | 0.94 |
| Arch of aorta | Mean | 0.83±0.2 | 0.79±0.16 | 0.3 | 0.88±0.24 | 1±0.48 | 0.16 | 0.31 |
| | pvcMean | 1.13±0.53 | 1.02±0.44 | 0.17 | 1.15±0.42 | 1.37±0.86 | 0.1 | 0.13 |
| | Max | 2.68±0.52 | 2.74±0.55 | 0.600 | 2.88±0.78 | 3.01±1.43 | 0.687 | 0.376 |
| | Total | 33.83(18.2-61.38) | 31.73(16.64-54.31) | 0.58 | 44.37(17.35-68.48) | 45.2(14.92-104.39) | 0.13 | 0.15 |
| | pvcTotal | 46.17(4.38-123.75) | 41.49(13.25-82.05) | 0.24 | 53.62(14.89-86.25) | 50.54(10.45-169.18) | 0.15 | 0.32 |
| Thoracic aorta | Mean | 0.92±0.2 | 0.87±0.2 | 0.08 | 0.99±0.24 | 1.06±0.43 | 0.98 | 0.43 |
| | pvcMean | 0.85±0.32 | 0.84±0.34 | 0.97 | 1.04±0.35 | 1.16±0.6 | 0.81 | 0.07 |
| | Max | 3.26±1.3 | 3.08±1.24 | 0.187 | 3.89±1.15 | 3.96±1.58 | 0.984 | 0.028 |
| | Total | 50.97(23.36-94.58) | 53.53(25.17-124.74) | 0.6 | 68.68(25.49-103.46) | 62.34(23.3-187.11) | 0.94 | 0.09 |
| | pvcTotal | 45.72(15.98-121.1) | 48.3(16.96-155.51) | 0.6 | 73.42(20.6-128.69) | 59.98(14.65-223.98) | 0.99 | 0.041 |
| Abdominal aorta | Mean | 0.94±0.2 | 0.92±0.19 | 0.33 | 1.04±0.28 | 1.1±0.53 | 0.97 | 0.55 |
| | pvcMean | 1.1±0.3 | 1.08±0.26 | 0.4 | 1.31±0.44 | 1.39±0.82 | 0.94 | 0.92 |
| | Max | 3.2±1.14 | 2.86±0.69 | 0.145 | 3.85±1.36 | 3.71±1.75 | 0.277 | 0.086 |
| | Total | 28.46(18.44-60.34) | 29.66(17.45-63.78) | 0.84 | 34.42(18.4-87.43) | 37.94(16.97-174.22) | 0.44 | 0.18 |
| | pvcTotal | 35.5(15.36-77.48) | 33.05(17.8-83.09) | 0.82 | 42.9(21.91-130.19) | 46.15(16.17-252.7) | 0.42 | 0.06 |
| Whole aorta | Mean | 0.89±0.18 | 0.86±0.17 | 0.14 | 0.97±0.23 | 1.05±0.46 | 0.66 | 0.43 |
| | pvcMean | 0.99±0.31 | 0.95±0.28 | 0.09 | 1.14±0.35 | 1.29±0.71 | 0.38 | 0.23 |
| | Max | 3.55±1.28 | 3.44±1.2 | 0.495 | 4.27±1.17 | 4.35±1.93 | 0.872 | 0.008 |
| | Total | 119.5±31.62 | 118.33±33.47 | 0.54 | 143.01±48.59 | 160.19±87.36 | 0.2 | 0.09 |
| | pvcTotal | 134.04±51.8 | 131.53±51.42 | 0.4 | 170.23±72.68 | 196.95±130.27 | 0.17 | 0.08 |

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Table 3 CT density in major arteries of health subjects and angina patients at baseline and 2-year follow-up.

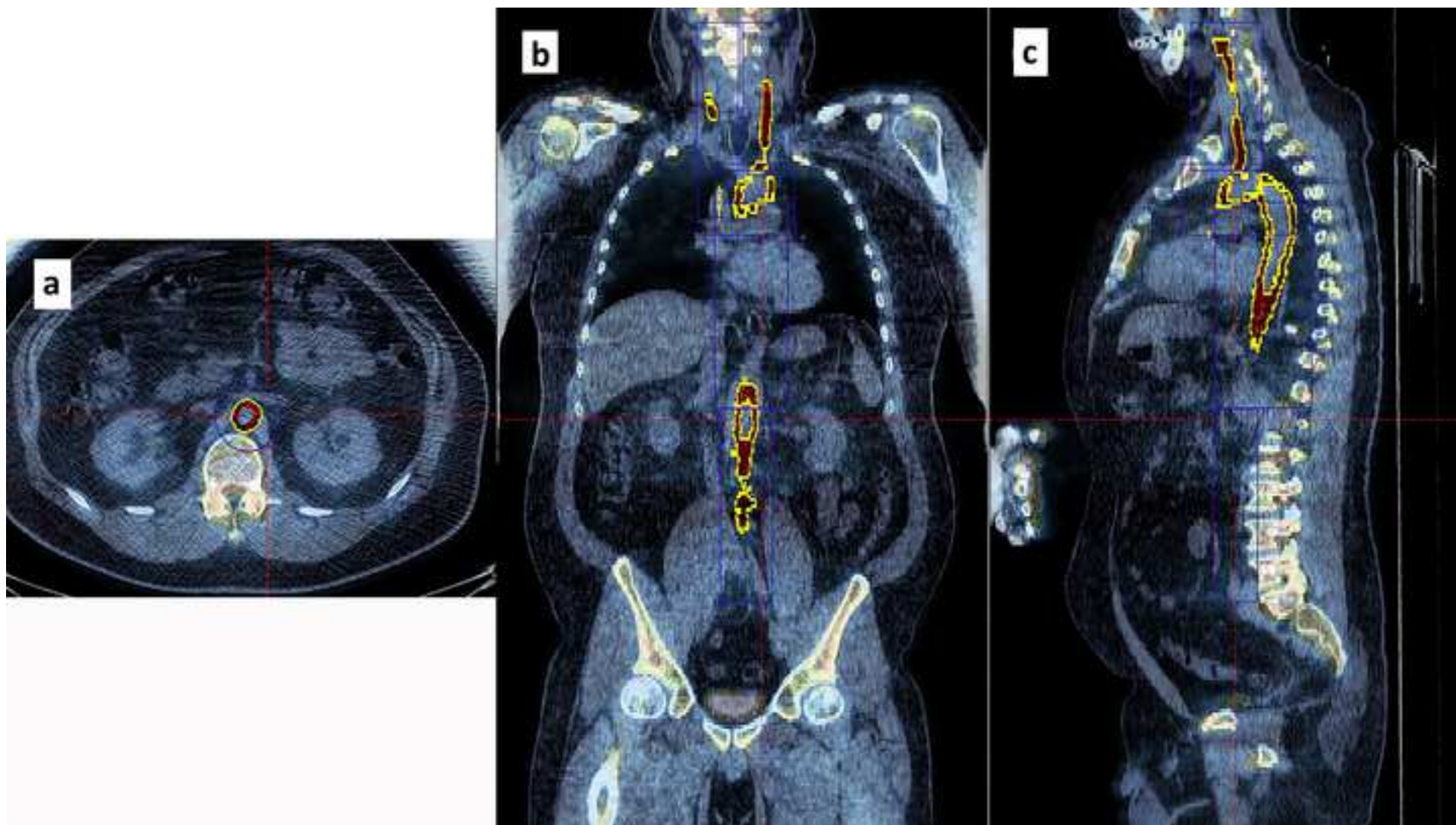
| Variable | | CT (HU) | | | | | | Baseline Angina vs. Healthy |
|-----------------|------|---------------------|--------------------|---------|---------------------|--------------------|---------|-----------------------------|
| | | Healthy (n=29) | | | Angina (n=20) | | | |
| | | Baseline | Follow up | P-value | Baseline | Follow up | P-value | |
| Left carotid | Mean | 24.39(8.5-39.36) | 23.37(9.1-36.47) | 0.6 | 18.17(3.13-41.93) | 17.83(4.52-36.46) | 0.47 | 0.009 |
| Right carotid | Mean | 38.02(13.86-47.51) | 37.17(12.94-50.1) | 0.85 | 34.98(22.34-47.61) | 37.37(21.87-49.24) | 0.049 | 0.43 |
| Carotids | Mean | 15.98(7.3-22.8) | 16.67(6.63-22.28) | 0.68 | 15.53(8.71-22.89) | 17.34(9.9-23.31) | 0.014 | 0.43 |
| Arch of aorta | Mean | 2.27(-21.42-21.6) | 1.8(-25.43-19.29) | 0.13 | -5.34(-19.79-11.28) | -1.89(-37.63-13.1) | 0.4 | 0.001 |
| Thoracic aorta | Mean | 4.46(-15.64-21.97) | 4.33(-13.21-16.76) | 0.84 | 1.14(-11.37-15.78) | 3.73(-15.9-16.89) | 0.42 | 0.8 |
| Abdominal aorta | Mean | 22(-3.07-63.29) | 22.67(-3.88-74.66) | 0.42 | 27.37(-3.3-95.98) | 26.08(19-114.18) | 0.34 | 0.23 |
| Whole aorta | Mean | 10.23(-99.47-20.35) | 8.17(-4.6-23.51) | 0.6 | 6.98(-4.53-26.29) | 7.71(-6.39-31.23) | 0.9 | 0.49 |

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Table 4 Correlation of age with NaF uptake (SUV) and density (CT) in major arteries.

| | | | SUV | CT | Z-score* | Pvalue |
|-----------------|-------|-------------------------|------------------|--------------|-------------|--------------|
| Right carotid | Mean | Correlation coefficient | 0.12 | 0.09 | 0.67 | 0.25 |
| | | Sig. (2-tailed) | 0.4 | 0.56 | | |
| | cMean | Correlation coefficient | 0.22 | | | |
| | | Sig. (2-tailed) | 0.12 | | | |
| Left carotid | Mean | Correlation coefficient | 0.05 | -0.03 | 0.89 | 0.19 |
| | | Sig. (2-tailed) | 0.76 | 0.82 | | |
| | cMean | Correlation coefficient | 0.18 | | | |
| | | Sig. (2-tailed) | 0.22 | | | |
| Carotids | Mean | Correlation coefficient | 0.12 | 0.11 | 0.39 | 0.35 |
| | | Sig. (2-tailed) | 0.43 | 0.44 | | |
| | cMean | Correlation coefficient | 0.20 | | | |
| | | Sig. (2-tailed) | 0.17 | | | |
| Arch of aorta | Mean | Correlation coefficient | 0.27 | -0.13 | 2.45 | 0.007 |
| | | Sig. (2-tailed) | 0.06 | 0.36 | | |
| | cMean | Correlation coefficient | 0.39 | | | |
| | | Sig. (2-tailed) | 0.006 | | | |
| Thoracic aorta | Mean | Correlation coefficient | 0.37 | 0.08 | 2.07 | 0.019 |
| | | Sig. (2-tailed) | 0.01 | 0.58 | | |
| | cMean | Correlation coefficient | 0.50 | | | |
| | | Sig. (2-tailed) | <0.001 | | | |
| Abdominal aorta | Mean | Correlation coefficient | 0.33 | 0.40 | 0.06 | 0.48 |
| | | Sig. (2-tailed) | 0.02 | 0.004 | | |
| | cMean | Correlation coefficient | 0.41 | | | |
| | | Sig. (2-tailed) | 0.003 | | | |
| Whole aorta | Mean | Correlation coefficient | 0.38 | 0.21 | 1.54 | 0.06 |
| | | Sig. (2-tailed) | 0.007 | 0.14 | | |
| | cMean | Correlation coefficient | 0.50 | | | |
| | | Sig. (2-tailed) | <0.001 | | | |

*The calculated Z-score refers to the comparison of age and pvcSUVmean correlation vs. age and CTmean correlation.



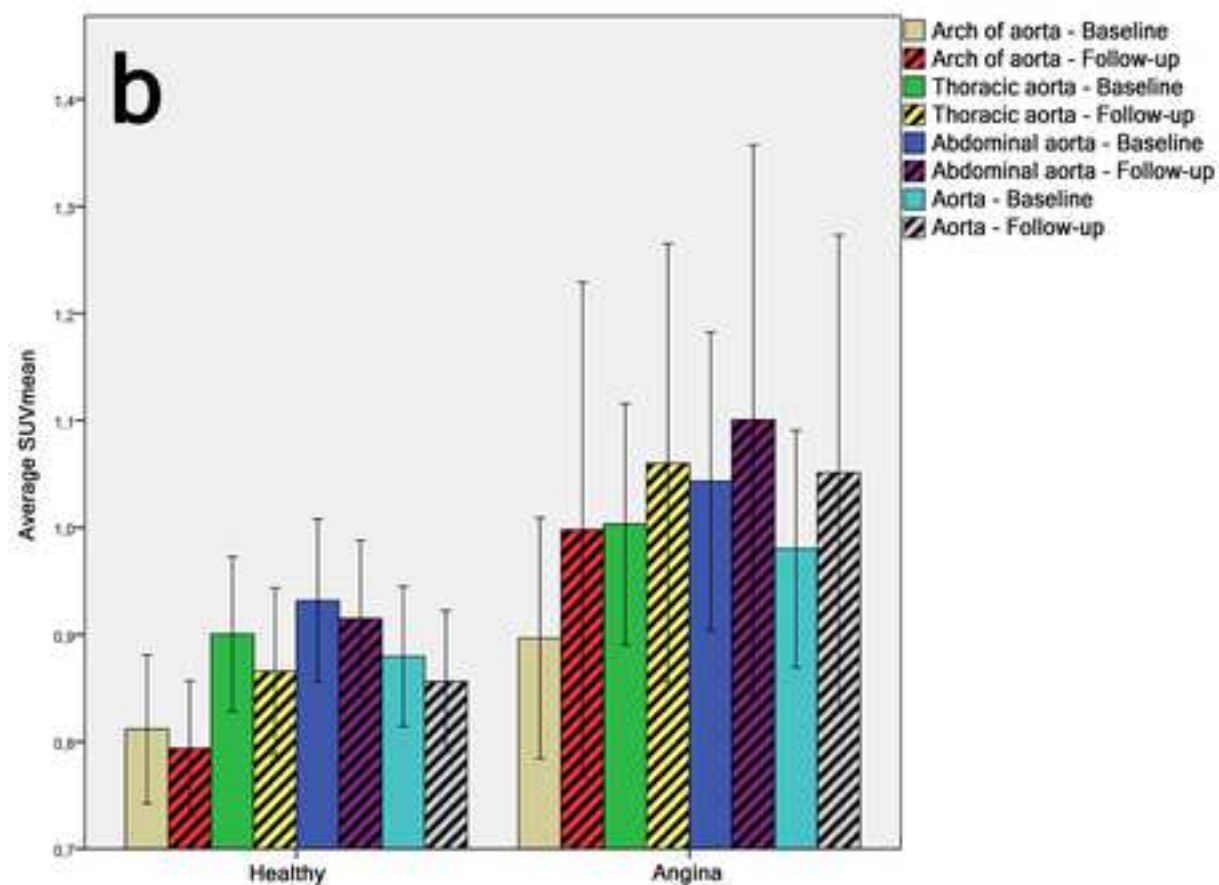
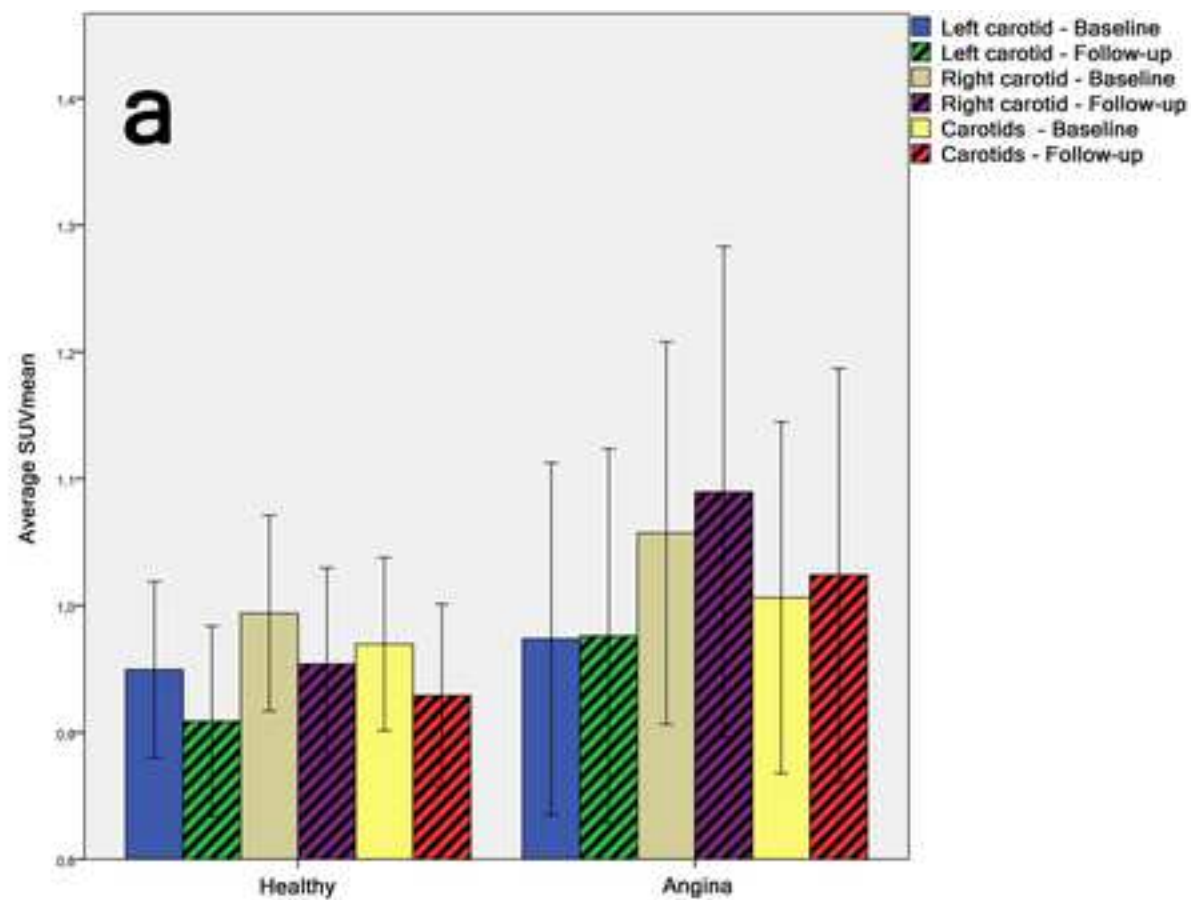
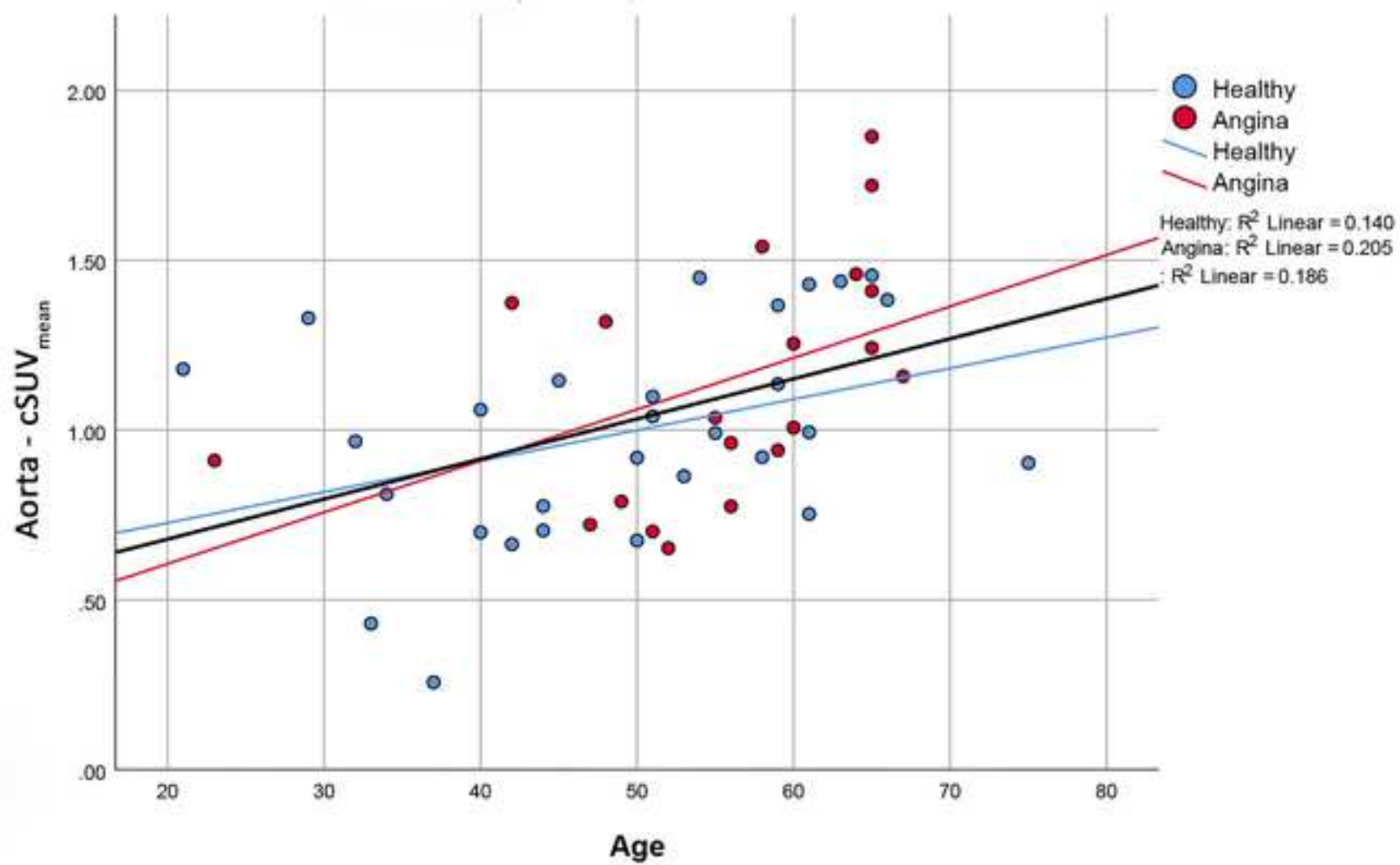


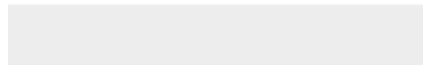
Figure 3





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